REMARKS

The Examiner has newly-rejected Claims 1-34 under 35 USC 103(a) over WO 98/43654 ("PCT Publication") in view of Cleveland *et al.* 6,048,901; Wood *et al.* 5,498,425; and Vining.

Wood et al. is relied upon for its disclosure of the use of cascara and biscodyl in bowel clearance. Vining is relied upon for its teaching that a bowel cleansing procedure can be accomplished with a clear liquid diet in conjunction with laxatives.

The Examiner relies upon the PCT Publication for its alleged teaching of a composition and method for purging the colon, comprising sodium phosphate salts combined with polyethylene glycol, biscodyl, and cascara, and administering the composition in solid or liquid form, referring to pages 1,7, and 11 of the Publication.

This Publication is directed to colonic purgative formulations in which are contained purgative active amounts of a salt selected from the group consisting of $Mg(PO_4)_2$, $MgHPO_4$, $Mg(H_2PO_4)_2$, $MgSO_4$, $MgCl_2$, $NaSO_4$, sodium tartrate, potassium tartrate, magnesium tartrate, and mixtures thereof in a stable, nonaqueous tablet dosage form (page 5, Brief Summary of the Invention). Except for the last claim, Claim 25, the composition claims recite "an orally administrable non-aqueous composition" comprising "a purgative effective amount" of a "non-aqueous admixture of a salt selected from the group consisting of $Mg(PO_4)_2$, $MgHPO_4$, $Mg(H_2PO_4)_2$, $MgSO_4$, $MgCl_2$, $NaSO_4$, sodium tartrate, potassium tartrate, magnesium tartrate, and mixtures thereof"; the method claims have similar recitations. The specification on pages 1-11 thereof contains a detailed description of methods for making and using these inventions, including tablet and capsule formulations with suggested adjuvants, recommended dosages, and dosage regimens.

Appended to these teachings in the penultimate paragraph bridging pages 11 and 12 of the specification, the Publication presents "another aspect of the invention", which

dispenses with the $Mg(PO_4)_2$, $MgHPO_4$, $Mg(H_2PO_4)_2$, $MgSO_4$, $MgCl_2$, $NaSO_4$, sodium tartrate, potassium tartrate, magnesium tartrate salts and mixtures thereof which constitute the gist of the Publication's compositions and methods and proposes that, "alternatively, the prior art [mono-, di-, and tribasic sodium] phosphate salts of Aronchick may be combined with any one or more of prior art purgative or laxative compounds or compositions including, for example: aqueous sodium phosphate salts, polyethylene glycol, aqueous polyethylene glycol, electrolyte solutions such as sodium sulfate, sodium bicarbonate, sodium chloride and potassium chloride, among others, including $Mg(OH)_2$, citrate salts such as magnesium citrate, lactate salts such as magnesium lactate, sorbitol, magnesium carbonate hydroxide, diphenyl methanes such as phenolpththalein [sic] and biscodyl, methyl cellulose, sodium carboxymethyl cellulose, psyllium (plantago) preparations, tragacanth and related natural gums, bran and other fibers, potassium sodium tartrate, castor oil, anthraquinones such as senna, cascara sagrada, aloe, and danthrone, dioctyl sodium sulfosuccinate, dioctyl calcium sulfosuccinate, and minerol [sic] oil among others, in effective amounts in order to produce a purgative and/or laxative composition which evidences synergistic activity in comparison to the prior art compositions or compounds which are used alone." [Emphasis added.} The desired activity is further defined in this paragraph as "potentially synergistic purgative activity".

Applicant notes that the priority document for the PCT Publication is USSN 08/829,080 filed 31 March 1997 which issued as US Patent 6,162,464; this patent does not contain the paragraph referred to above (or any other discussion of the material in this paragraph), and on its face this material constitutes an Addendum to the subject matter of the priority document prior to filing the corresponding PCT. This portion of the Publication is hereinafter referred to as "the Addendum" which, it is submitted, is the only portion of this Publication relevant to the prosecution of this matter.

It is Applicant's position that this disclosure does not establish a *prima facie* case of obviousness of Applicant's inventions over this prior art.

The controlling law has been stated thusly [MPEP 2141.02,1 citing In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d, 1442 1448 (Fed.Cir. 1991)]: "...A proper obviousness analysis requires consideration of 'whether the prior art would also have revealed that in so making or carrying out [the claimed invention], those of ordinary skill in the art would have a reasonable expectation of success.'" or, "...whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process." or, citing In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988), "...'The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art.'"

Applicant's claims broadly comprise dry bowel-cleansing compositions (dry 'prep' compositions) comprising a sodium phosphate powder and water-soluble or water-miscible polyethylene glycol in specified proportions, such compositions dissolved in water for oral administration, and methods for using these compositions. As discussed in the specification and evidenced in the Examples, the compositions are very acceptable to patients, with mild or no side effects; there is also high patient compliance with the preps and efficacy scaling from good to excellent in the clinical studies.

The PCT Publication Addendum teaches that sodium phosphate powders can be combined with "any one or more of prior art purgative or laxative compounds or compositions" in "effective amounts" to obtain compositions having "potentially synergistic purgative activity" (emphasis added; page 11, lines 4-7 and 11-13). This enormous genus (prior art purgative and

laxative compounds or compositions) is exemplified by 9 subgenuses embracing an unknown number of species plus 27 species including polyethylene glycol and aqueous polyethylene glycol as representative prior art purgative or laxative compounds or compositions which may be combined with the phosphate powders in an attempt to find compounds actually having "synergistic purgative activity" (page 11, lines 13-22).

What in this Addendum would motivate one skilled in the art to make Applicant's claimed compositions or carry out Applicant's claimed processes as a whole? According to In re Vaeck, *op.cit.*, "In order to find such motivation or suggestion there should be a reasonable likelihood that the claimed invention would have the properties disclosed by the prior art teachings." Here, there is not even the reasonable likelihood that any of the dozens of compositions proposed in the Addendum has the disclosed property of "potential synergistic purgative activity" and there is thus no reason to make any of them, including Applicant's claimed compositions. Not one of the proposed compositions has been shown to have this property. It is not even certain what this property is in the present context. The only relevant prior art teaching is that one or more of the dozens or possibly hundreds of purgatives or laxatives known in the prior art might have "synergistic" purgative activity when combined with sodium phosphate powders, in comparison with such purgative or laxative when used alone. The teachings offer no guidelines whatsoever for e.g., selecting one candidate laxative/purgative over another for testing from the huge pool of largely chemically unrelated candidates suggested, nor for calculating proportions of candidates and sodium phosphate powders to be combined, nor for calculating dosages, nor for determining potentially harmful or fatal combinations of purgatives.

The specification outside the Addendum cannot be of assistance as that only describes making and using non-sodium-phosphate salts, preferably magnesium phosphate salts, as

purgatives (*supra*). Illustrative methods and/or materials for making and using non-sodium-phosphate salts in compositions with "numerous other purgative salts and/or laxative compounds" (page 10, lines 24-27) are entirely lacking. While the Examiner points out that the Addendum states that one of ordinary skill in the art may readily determine the amounts and types of compounds/compositions to be used in treating a particular patient, this is common boilerplate language typically used when the patentees do not know themselves. And, as discussed above, it is not true.

Even assuming *arguendo* that at least one composition could assuredly be found in this pool having some kind of "synergistic purgative activity", why would one skilled in the art be motivated to test dozens of compositions in search of this needle in a haystack? Sodium phosphate powder is a well-known purgative, and some additional purgative activity would be expected to be eventually obtainable by combining a given amount of this powder with various trial amounts of some other purgative or laxative. Even if this purgative activity were found to be "synergistic", why bother? The primary problem with currently commercially available purgatives, including sodium phosphate powders and polyethylene glycol with electrolytes as described in Applicant's specification, is not their "purgative activity", it is their side effects such as nausea, cramping, diarrhea, vomiting, bloating, dehydration, and difficulty with administration which lead to non-compliance by patients, who then take too little of the necessary dosage, which in turn leads to insufficient bowel cleansing. None of these issues are even discussed in this Addendum. As reported (MPEP 2141.02 IIA14(d), "Lack of any known useful properties weighs against a finding of motivation to make or select a species or subgenus."

The sole disclosure of a composition according to this Addendum is found in Claim 25. Although the Addendum vaguely states that the sodium phosphate mixtures can be administered as liquids or solid form, Claim 25 defines a selected composition

as "an orally administrable non-aqueous composition... comprising a purgative effective amount of a nonaqueous admixture of a sodium phosphate salt ...in combination with an effective amount of at least one composition selected from the group consisting of aqueous sodium phosphate salts, polyethylene glycol, aqueous polyethylene glycol, aqueous solutions of sodium sulfate, sodium bicarbonate, sodium chloride or potassium chloride, $Mg(OH)_2$, citrate salts such as magnesium citrate, lactate salts such as magnesium lactate, sorbitol, magnesium carbonate hydroxide, phenolpththalein [sic], biscodyl, methyl cellulose, sodium carboxymethyl cellulose, psyllium, tragacanth, bran, potassium sodium tartrate, castor oil, senna, cascara sagrada, aloe, danthrone, dioctyl sodium sulfosuccinate, dioctyl calcium sulfosuccinate, minerol [sic] oil, and mixtures, [sic] thereof." [Emphasis added.]

This is to say, a non-aqueous composition comprising a non-aqueous admixture of sodium phosphate salt and at least one member of 3 subgenuses and 27 species and mixtures thereof which is orally administrable in a purgative-effective amount.

In this embodiment, aqueous polyethylene glycol cannot be considered as a candidate for admixture with the sodium phosphate salt because the phosphate salt admixture and the composition for oral administration must both be non-aqueous according to the claim description. Nor can non-aqueous polyethylene glycol be considered as a candidate for admixture with a sodium phosphate salt in a purgative-effective amount to form an orally administrable non-aqueous composition according to this claim description, as it is highly unlikely that a purgative effective dry mixture of phosphate and PEG could be both safely and comfortably orally administered, and no evidence that this can be done is offered. As this Claim presumably represents a preferred form of the composition, it is submitted that the prima facie inoperabilities of these species would completely discourage one skilled in the art from selecting either aqueous or nonaqueous polyethylene glycol as a suitable

purgative or laxative for combination with the sodium phosphate salt to obtain "synergistic purgative activity". The Examiner is requested to note that Applicant's dry compositions comprising specified proportions of sodium phosphate salts and water-soluble polyethylene glycol are not suitable for oral administration: they must first be dissolved in an aqueous liquid in specified dosage amounts as described and claimed in the present application. For example, an exemplary formulation on page 5 of Applicant's specification for a single dose drink, 60 g. PEG and 18 g. phosphate powder, is dissolved in 1-1.5 quarts water for administration. It cannot be imagined that this dry phosphate/PEG mixture could be ingested as a single dose. Also, Applicant's aqueous compositions and methods for oral administration are outside the scope of Claim 25, which requires non-aqueous compositions for direct oral administration.

Referring to MPEP 2141.02 IIA, it is stated that, "When evidence of secondary considerations such as unexpected results is initially before the Office, for example in the specification, that evidence should be considered in deciding whether there is a *prima facie* case of obviousness."

Applicant's specification emphasizes the very good efficacy in conjunction with significantly improved patient compliance obtained by practicing the claimed inventions, as compared to prior art purgatives such as sodium phosphate and polyethylene glycol/electrolyte purgatives used alone Evidence of efficacy and compliance includes 6 clinical studies with post-prep colonoscopy photographs for each study. In each case, adequate to good views of the colon were reported in the text and/or corresponding photographs. Also, no incidents of nausea, vomiting, cramping or diarrhea were reported by any of these patients. Two patients had mild complaints of the taste of the composition, and the rest of the patients had no complaints. There is nothing in any of the prior art cited by the Examiner, and in particular the PCT Publication, which even slightly suggests that any such unexpected and unobvious results might be

obtained by combining and using these two known laxative/purgatives as described in the specification and set forth in Applicant's claims.

It is accordingly respectfully submitted that a case of *prima facie* obviousness over the cited art has not been established, and reconsideration and withdrawal of this ground of rejection is respectfully requested.

In the event that *prima facie* obviousness is deemed to be shown, Applicant offers the following additional remarks and iterates all or some of the above Remarks in rebuttal:

Applicant's claims broadly comprise dry bowel-cleansing compositions (dry 'prep' compositions) comprising a water-soluble sodium phosphate powder and water-soluble polyethylene glycol in specified proportions, such compositions dissolved in water or other aqueous liquid for oral administration, and methods for using these compositions. As discussed in the specification and evidenced in the Examples, the compositions are very acceptable to patients, with at most mild or no side effects and adequate palatability. Accordingly, in use, there is also high patient compliance, demonstrated by cleansing efficacy which scaled from adequate to good to excellent in the clinical studies. This is in direct contrast to the individual components' side effects when used above; as described on page 2 of the specification, phosphate purgatives are associated with nausea, vomiting, and poor taste, while PEG purgatives also have an unpleasant taste and require large amounts of fluid carrier which can cause bloating and nausea. As evidence of these side effects, Applicant submits herewith extracts from two health care websites (UConnHealthCenter http://health.uchc.edu/clinicalservices; http://NetDoctor.co.uk/medicine) which describe these symptoms in detail (Exhibit A). Applicant also submits herewith so-called "package inserts" for Fleet Phospho-Soda laxative (sodium phosphate preparation) and Golytely (PEG bowel cleansing preparation (Exhibit B).

Applicant further submits Exhibit C, which reports clinical studies conducted by the present inventor using known PEG and sodium phosphate and bowel cleansers as comparisons to the PEG/phosphate cleansers of the present invention (Examples). The comparison studies consistently report bad taste, abdominal pain, nausea, and/or bloating in contrast to the results obtained by the use of compositions according to the present invention. An Affidavit by the inventor accompanies Exhibit C.

Applicant has found no "synergetic purgative activity." Applicant has found a combination of bowel cleansing components which unexpectedly provides effective cleansing, significantly reduces common side effects of each of the components, and are palatable greatly improving patient compliance.

With respect to the Wood et al. '425 and Vining references, Applicant is not urging the patentability of biscodyl, cascara, or clear liquid diets per se, but each in combination with Applicant's novel PEG/sodium phosphate compositions. Cleveland et al. teaches the use of polyethylene glycol to treat symptoms of constipation, specifically, cramps and anal irritation. Nausea, vomiting, abdominal pain, and bloating are not mentioned. Cleveland et al. does not so much as mention bowel cleansing, nor methods for alleviating side effects and unpalatability of bowel cleanser. Clearly, there is no reason for one skilled in the art to combine this reference with the teachings of the PCT application. Further, according to the Examiner, the Cleveland et al. composition should be free of ancillary electrolytes as the salt may exert a constipative effect. This of course teaches against the use of a combination of PEG and sodium phosphate salts (electrolytes) for bowel cleansing. This reference appears to have, at best, only a peripheral relevance to the prosecution of the present application.

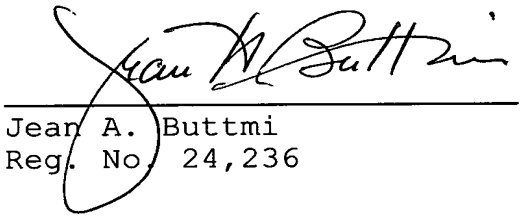
Claims 1 and 13 have been amended to clarify that the phosphate powder is also readily water-soluble, to provide a composition wherein the active ingredients can be admixed with

an aqueous medium to obtain a substantially homogenous and palatable drink. Preferably, any other additives are also water-soluble, but this is not required.

Antecedent basis for the amendment to claims 19-21 is found on page 6 of the disclosure.

In view of the above remarks and cited evidence, reconsideration and withdrawal of the present rejection of all the claims under 35 USC 103 for obviousness is respectfully requested and an early notice of allowability earnestly solicited.

Respectfully submitted,



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